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Sexual Processes in Microbial Eukaryotes

Harris Bernstein and Carol Bernstein

Abstract

Two principal ideas have been proposed to explain the primary adaptive function of the sexual process of meiosis: (1) meiosis, and particularly meiotic recombination, is a process for repairing DNA and (2) meiosis, by means of meiotic recombination, is a process for generating beneficial genetic variation among progeny. We review the sexual processes of a number of well-studied microbial eukaryotes: *Saccharomyces cerevisiae*, *Saccharomyces paradoxus*, *Schizosaccharomyces pombe*, *Candida albicans*, *Ustilago maydis*, *Paramecium tetraurelia*, *Volvox carteri*, *Trypanosoma brucei*, *Neurospora crassa*, and *Amoebozoa*. We indicate aspects of the sexual processes of these microbial eukaryotes, where they have been established, that support the idea that meiosis is primarily a process for repairing DNA. In addition, we review the likely origin of meiotic sex among the microbial eukaryotes. A prokaryotic archaeon is the likely ancestor of eukaryotes. Extant archaea are capable of a sexual process involving syngamy and recombinational repair of genome damage, suggesting that the precursor of eukaryotic meiotic sex may already have been present in the archaeal ancestor of eukaryotes. We believe that attainment of an understanding of the adaptive function of meiotic sex in microbial eukaryotes is of considerable importance since it will likely apply to meiotic sex in eukaryotes generally.

Keywords: meiosis, adaptive benefit, DNA repair, homologous recombination, genetic variation

1. Introduction

Different microbial eukaryotic species are capable of a variety of sexual processes. Basically, however, the different sexual processes have, as a central element, syngamy and meiosis. Syngamy is the fusion of two cells or two nuclei. Meiosis is ordinarily initiated in a diploid cell that contains a pair of homologs, which is two copies of each chromosome. In meiosis, generally, first the cell undergoes DNA replication, so each homolog now consists of two identical sister chromatids. Next, homologous chromosomes undergo intimate pairing with each other and exchange genetic information by homologous recombination. Recombination is succeeded by two cycles of cell division to yield four haploid daughter cells each having half the number of chromosomes as the original diploid cell. Some microbial eukaryotes, however, use a similar process, parasexual meiosis. This is where ploidy (the number of complete sets of chromosomes in a cell) is determined, both before and after homologous recombination, by processes other than those in standard meiosis. One of the microbial eukaryotes we discuss, below, *Candida albicans*, uses parasexual meiosis.

There appears to be broad agreement among geneticists that the key to understanding why sex exists is to understand the adaptive benefit of meiotic homologous recombination, the molecular event that syngamy and meiosis seem designed to promote. The evidence reviewed here on microbial eukaryotes, we think, supports the general view that the meiotic recombination mechanism is maintained by natural selection at each generation because of the benefit of DNA repair [1]. Recombinational repair is especially beneficial as an adaptation for responding to stressful conditions, such as starvation or oxidative stress, that cause DNA damage.

Meiotic sex appears to be very widespread among microbial eukaryotes. In 1999, Dacks and Roger [2] proposed, on the basis of phylogenetic evidence, that the common ancestor of all known eukaryotes was likely facultatively sexual. Since this proposal was presented, sex has been reported in several microbial eukaryotes that had previously been considered to be asexual. Examples of organisms recently recognized to be sexual are *Giardia intestinalis* (syn. *G. lamblia*) and *Trichomonas vaginalis*. These microbial eukaryotes were found to possess a core set of genes that function in meiosis, including genes that encode proteins that are specific to meiosis and act in homologous recombination [3, 4]. Both *G. intestinalis* and *T. vaginalis* are descended from ancient lineages that diverged from each other early in the evolution of eukaryotes, thus indicating that core genes necessary for meiosis, and hence sex, were likely present in an early ancestor of both species. Parasitic protozoans of the genus *Leishmania* are another example of eukaryotic microbes once considered to be asexual, but subsequently found upon further investigation, to have a sexual cycle [5]. Also, evidence for meiotic sex has recently been reported for the phylum *Amoebozoa*, another early diverging lineage in eukaryotic evolution (see Section 10). Fungi, a diverse group of eukaryotic microorganisms, also appear to be anciently sexual [6]. Recent findings on additional species, reviewed by Speijer et al. [7], also tend to substantiate the concept that sex is an ancient, ubiquitous and fundamental feature of eukaryotic life. Such varied reports have contributed to the current understanding that meiotic sex is likely a fundamental and primordial property of eukaryotes (e.g. [3, 4, 8]).

We describe here the typical stages of the sexual cycles of eukaryotic microbes, although the amount of time spent in each stage is variable among species. The stages are: (1) Haploid cells reproduce by mitosis (vegetative growth). (2) Haploid cell undergo cellular fusion (syngamy) to form a heterokaryon that may undergo further mitotic divisions (vegetative growth). (3) A diploid cell is formed when two haploid nuclei fuse. Diploid cells may also undergo additional mitotic divisions (vegetative growth). (4) The meiotic process is initiated in the nucleus of a diploid cell by undergoing a round of DNA replication without cell division, so that the nucleus has four copies of its genome. Conventionally, the nucleus at this stage is described as having two sets of homologous chromosomes where each chromosome is composed of two sister chromatids (a chromatid being equivalent to a long DNA molecule bound with appropriate histone proteins). (5) Homologous chromatids undergo intimate pairing (synapsis) including pairing of non-sister homologous chromatids. (6) Genetic information is exchanged between the paired homologous chromatids by a process of recombination. Recombination may involve breakage and exchange between paired chromatids, but in most cases information is exchanged without breakage and exchange by a process referred to as synthesis dependent strand annealing [9]. (7) Meiosis is completed by two successive cell divisions whereby a cell nucleus, starting with four copies of the genome, produces four cell nuclei each having a single copy of the genome. During the first meiotic division chromosome segregation occurs so that after completion of the division there is one set of chromosomes (each with two chromatids) in each cell nucleus. During the second meiotic division there is only one set of chromatids (each

chromatid, now renamed as a chromosome, in each cell nucleus). That is, haploidy is restored. In parasexual meiosis, control of ploidy both before and after homologous recombination may occur by processes other than those in “standard” meiosis (see Section 5). The life cycle may now be repeated starting at stage (1).

2. *Saccharomyces cerevisiae* and *Saccharomyces paradoxus*

The budding yeast *S. cerevisiae* (Figure 1A) is a microbial fungus in the Division *Ascomycota*. *S. cerevisiae* occurs in nature as haploid (n) or diploid (2n) cells (Figure 1B). Haploid vegetative cells can reproduce by mitosis under favorable conditions. Diploid cells can also reproduce by mitosis when nutrients are abundant. However, when quiescent *S. cerevisiae* are starved, they accumulate DNA damages that include double-strand breaks and apurinic/apyrimidinic sites [10]. *S. cerevisiae* cells maintained in a non-replicating quiescent state undergo chronological aging

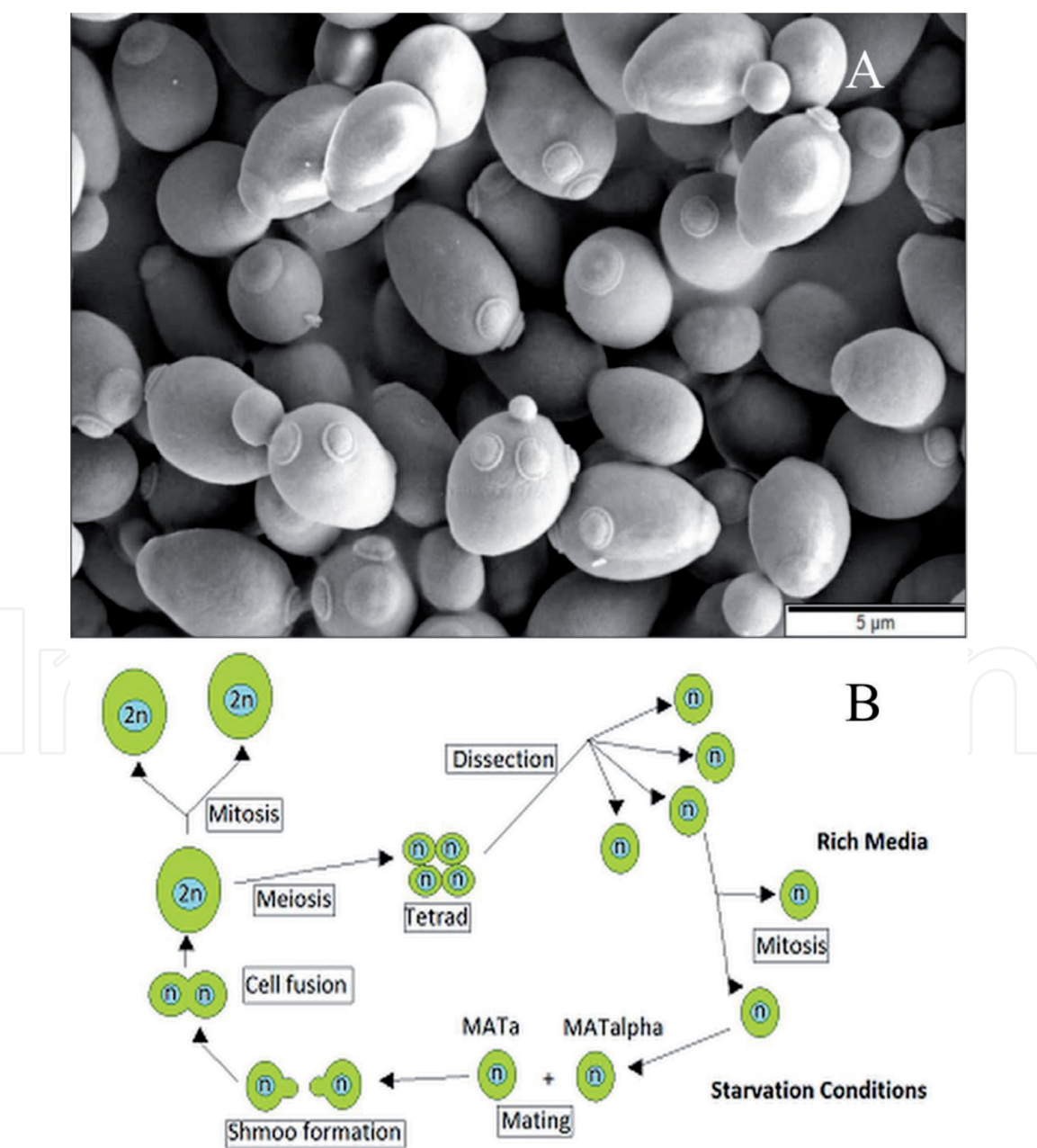


Figure 1.
(A) Budding yeast *Saccharomyces cerevisiae* [13] and (B) cycle of sexual and vegetative reproduction *S. cerevisiae* [14].

during which they accumulate DNA double-strand breaks and their ability to repair such damages declines [11]. When starving (and accumulating DNA damages), haploid cells can mate to form diploid cells that can undergo meiosis to produce four haploid spores that are contained within a sac-like structure, the ascus (tetrad) [12] (**Figure 1B**). Such spores are resistant to stress, but under favorable conditions can germinate to produce haploid descendants by mitosis. When haploid cells of mating type MATa and MAT α come into contact with each other they can fuse to form a diploid cell (syngamy) that may then either reproduce by mitosis or, if stressed, initiate another sexual cycle by undergoing meiosis. Recombination between homologous chromosomes is a central feature of meiosis and involves the systematic intimate pairing of homologous chromosomes. This process facilitates recombinational repair of DNA damages [9].

Increased sensitivity to killing by DNA damaging radiation or DNA damaging chemicals is a general characteristic of *S. cerevisiae* mutants that are defective in genes necessary for meiotic and mitotic recombination [15]. As an example, *Rad52* mutants of *S. cerevisiae* are deficient in meiotic and mitotic recombination and have increased susceptibility to killing by X-rays, methyl methanesulfonate and agents that introduce DNA crosslinks [15–17]. Homologous recombination is also necessary for recovery from oxidative DNA damage [18]. Such results demonstrate that DNA damages caused by diverse agents can be removed by recombinational repair.

A major effect of X-irradiation is the introduction of double-strand breaks in DNA. *S. cerevisiae* diploid cells in mitotic G1 phase are unable to repair such lethal X-ray induced damages [19]. However, *S. cerevisiae* cells in the G1 phase of meiosis are more resistant to the lethal effect of X-rays than cells in the mitotic G1 phase [19]. This suggests that X-ray induced lethal DNA damages are more efficiently repaired when occurring in meiotic G1 compared to mitotic G1. The increased resistance of cells undergoing meiosis may be explained by the intimate pairing of homologous chromosomes during meiosis which facilitates the replacement of damaged sequence information in one homolog by intact information from the other homolog.

Another proposed benefit of meiotic recombination, aside from DNA repair, is the production of progeny of varied genetic constitution, as occurs in outcross matings between unrelated individuals.

A study of the ancestry of natural *S. cerevisiae* strains indicated that outcrossing to an unrelated strain occurs only about once every 50,000 cell divisions [20]. That is, in nature, *S. cerevisiae* outcrossing is rare and mating is ordinarily between closely related cells. In nature, matings of *S. cerevisiae* tend to be between close relatives for two reasons [20]. First, the products of individual meiotic events are contained within the sac-like ascus, and each ascus contains a tetrad of ascospores, two ascospores of each mating type. Cells of different mating type from the same ascus tend to mate with each other because of their proximity, and such matings are between closely related individuals, which may not yield much, if any, genetic variation among the progeny. The second reason that mating tends to occur between genetically close relatives is mating type switching. Here, a cell of one mating type, upon mitotic cell division, produces two cells, usually one of the same mating types as the original cell and, often, a second cell of the opposite mating type. These two cells are physically adjacent and can mate with each other. Thus, in nature, the sexual cycle of *S. cerevisiae* can provide the benefit of recombinational repair, but only infrequently provides genetic variation.

In natural populations of the species *Saccharomyces paradoxus*, a sister species of *S. cerevisiae*, the frequency of matings between meiotic products from the same tetrad is estimated to be about 94% [21]. Also about 5% of matings are between clone-mates after switching of mating type. Only 1% of matings appear to be

outcrossings. Outcrossing, in principal, may provide the adaptive benefit of generating beneficial genetic variants. Nevertheless, the low frequency of outcrossing in natural populations of *S. cerevisiae* and *S. paradoxus* indicates that the production of genetic variation is unlikely to be the principal selective force maintaining meiotic sex in these organisms. On the other hand, meiosis facilitates homologous recombinational repair of DNA damages and such repair is especially beneficial under stressful conditions that are likely to be common in nature. This proposed benefit is compatible with the hypothesis that, in general, the principal selective force maintaining meiotic sex is DNA repair [1, 22, 23].

3. *Schizosaccharomyces pombe*

S. pombe, also referred to as “fission yeast,” is a unicellular rod-shaped eukaryotic microorganism in the Division *Ascomycota*. It grows vegetatively primarily as a haploid organism. *S. pombe* is facultatively sexual, so that when nutrients are limiting cells of opposite mating type tend to undergo syngamy (union of gametes) to form diploid zygotes [24]. The zygote can then enter meiosis leading to the production of four haploid products (spores) initially enclosed in a sac called an ascus.

Several different types of experiments have shown that DNA damages induce the sexual cycle and meiotic recombination in *S. pombe*. First, exposure of *S. pombe* cells to hydrogen peroxide, a reactive chemical that causes oxidative DNA damage, was observed to lead to an increase in sexual reproduction associated with a 4- to 18-fold increase in the formation of meiotic spores [25]. Second, DNA damages, in which the base cytosine is deaminated to uracil, forming the inappropriate base pair dU:dG, stimulate meiotic recombination [26]. Third, faulty processing of DNA replication intermediates (referred to as Okazaki fragments) produces DNA damages, including single-strand breaks or gaps, that stimulate meiotic recombination [27].

The fission yeast *S. pombe*, like the budding yeast *S. cerevisiae* (see above), switches mating type during vegetative growth, though they each use different mechanisms [28]. This provides *S. pombe* with increased mating opportunities with close relatives. The decreased opportunity for outcrossing in *S. pombe* indicates that the production of genetic variation is unlikely to be the principal selective force maintaining meiotic sex in these organisms. Overall, the findings with *S. pombe*, like those with the other yeasts, *S. cerevisiae* and *S. paradoxus*, suggest that meiotic recombination is primarily an adaptation for repairing DNA damage.

4. *Ustilago maydis*

U. maydis is a fungus in the Division *Basidiomycota*. It is a plant pathogen that causes corn smut. *U. maydis* teliospores are thick-walled rounded melanized cells with diploid nuclei that are capable of tolerating extreme temperatures and desiccation. Before teliospores mature in the infected corn plant, meiosis is initiated [29]. As teliospores germinate they complete meiosis to produce four haploid basidiospores [29].

Plants often defend themselves from pathogenic microbial invasion by releasing an oxidative burst that includes the production of reactive oxygen species [30]. *U. maydis* can protect against the host oxidative attack by an oxidative stress response [30]. In protecting against oxidative DNA damage, *U. maydis* employs a recombinational DNA repair system that includes the Rad51 protein (related to mammalian

Rad51), a Rec2 protein (more distantly related to mammalian Rad51), and the Brh2 protein [that is related to the mammalian Breast Cancer 2 (Brca2) protein]] [31]. When any of these proteins is inactive, *U. maydis* becomes more sensitive to DNA damaging agents, mitotic recombination is reduced, and there is failure to complete meiosis [31]. Recombinational repair occurring during meiosis as teliospores are formed by the pathogen likely contributes to the maintenance of its genome integrity by removing DNA damages incurred during infection.

5. *Candida albicans*

Candida albicans, a type of diploid yeast in the Division *Ascomycota*, is the most commonly encountered fungal pathogen in humans. The human infection candidiasis, resulting from overgrowth of *C. albicans*, often occurs in immunocompromised patients [32]. *C. albicans* can be induced to undergo a parasexual cycle that involves mating of diploids (syngamy) to form a tetraploid that subsequently appears to undergo a form of meiosis, followed by chromosome loss leading to approximately diploid cells with high levels of aneuploidy and homozygosity [33]. The *C. albicans* genome contains many genes that are homologous to genes in other species that function in meiosis [34]. One such gene, *Dmc1*, encodes a protein that has a central role in homologous recombination and is only known to express during meiosis [35]. Under appropriate conditions, *C. albicans* is capable of same sex mating and can undergo extensive genetic recombination between homologous chromosomes [36]. The two successive cell divisions that ordinarily occur subsequent to meiotic recombination in other organisms appear to be absent in *C. albicans* meiosis. Instead a reduction from four copies of the genome (tetraploidy) to two copies (diploidy) occurs by random chromosome loss during the mitotic cell division subsequent to meiotic recombination [37]. Although *C. albicans* populations are largely clonal, parasexual recombination can facilitate the evolution of resistance to the antifungal agent fluconazole upon exposure to the agent over successive generations [38].

The parasexual cycle appears to occur with greater frequency under environmental stress condition [33]. Glucose starvation and oxidative stress are environmental stresses that are commonly encountered by pathogenic *C. albicans*, and these stresses efficiently induce same-sex mating between cells from a single progenitor [39]. As suggested by Guan and collaborators [39], same sex mating in *C. albicans* may be an important mode of sexual reproduction that occurs often in nature. Oxidative stress, associated with an increase in reactive oxygen species, causes DNA damage and thus the induction of mating may reflect an adaptive DNA repair response.

Unlike *C. albicans*, several other *Candida* clade species have a sexual cycle that includes ordinary meiosis and formation of sexual spores [37]. It appears that *C. albicans* has retained meiotic homologous recombination, a principal feature of sexual reproduction that provides the adaptive benefit of DNA repair, while losing the ability to undergo successive cell divisions in an organized fashion to reduce ploidy.

6. *Paramecium tetraurelia*

P. tetraurelia is a unicellular eukaryotic ciliate in the Phylum *Ciliophora* (Figure 2). It has two diploid micronuclei and a polyploid macronucleus. The

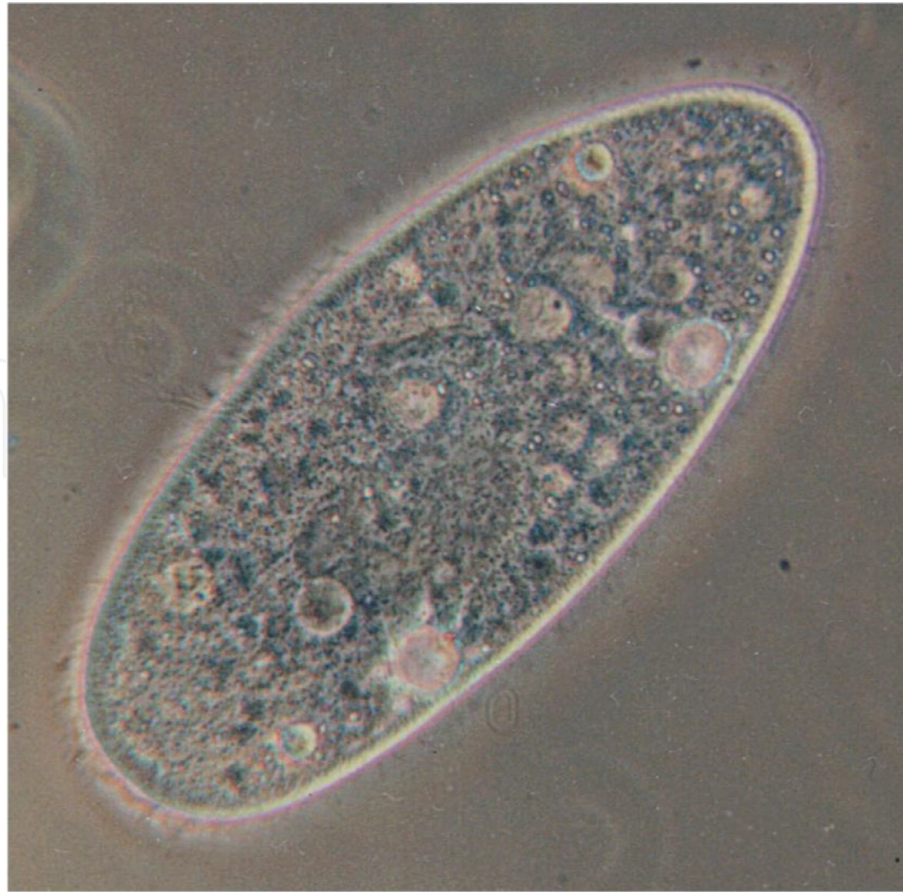


Figure 2.
Paramecium tetraurelia [41].

micronuclear chromosomal DNA contains the genetic information that is inherited from one generation to the next, whereas the macronucleus contains many chromosomal DNA copies that express cellular functions. *P. tetraurelia* is able to undergo both asexual and sexual reproduction. Asexual reproduction occurs by binary fission in which the micronuclei divide by mitosis and the macronucleus divides by amitotic division [40]. Sexual reproduction involves a meiotic process, either automixis or conjugation. Automixis is a kind of self-fertilization, whereas conjugation involves mating with another individual.

As *P. tetraurelia* undergoes asexual reproduction by binary fission over many successive generations, the vitality of the lineage declines (clonal aging) until the lineage reaches the end of its clonal lifespan at about 200 fissions [42]. However, if *P. tetraurelia* undergoes automixis or conjugation during clonal aging, vitality is restored. Several laboratories found that clonal aging is associated with a dramatic increase in DNA damage [42–44]. When clonally aged *P. tetraurelia* undergo automixis or conjugation, the micronuclei go through meiosis followed by pairwise nuclear fusion (syngamy) of haploid meiotic products either from the same individual (automixis) or from different individuals (conjugation) to form a new diploid micronucleus. Subsequent to the formation of a new diploid micronucleus, the old macronucleus disintegrates and the new micronucleus replicates to form a new macronucleus. The paramecia that undergo this process have their clonal lifespan restored and are rejuvenated. Clonal aging thus appears to be caused to a large extent by progressive accumulation of DNA damage and rejuvenation likely depends on the repair of such damages in the micronuclear DNA during meiosis followed by the reestablishment of macronuclear DNA by replication of the newly repaired micronuclear DNA.

7. *Volvox carteri*

Volvox carteri is in the Phylum *Chlorophyta*. It is a facultatively sexual species of colonial green algae. The *V. carteri* life cycle can include both a sexual and asexual phase. Under natural conditions, *V. carteri* reproduces asexually in temporary ponds during the spring. However, before the ponds dry up in the summer heat, it becomes sexual forming male and female gametes which can then undergo fertilization to form a desiccation resistant overwintering diploid zygospore. Germination of zygospores involves meiosis and takes place when environmental conditions become favorable, usually the next spring.

V. carteri can be induced by heat shock to undergo sexual reproduction [45]. Antioxidants can inhibit this induction, indicating that oxidative stress likely mediates the induction of sexual reproduction by heat shock [46]. Also implicating oxidative stress is the finding that an inhibitor of the mitochondrial electron transport chain, that causes an increase in reactive oxygen species, induces sex in *V. carteri* [47]. Thus the induction of facultative sex, even under natural conditions, may be due to oxidative stress, a condition that causes oxidative DNA damage [47].

8. *Trypanosoma brucei*

Human African trypanosomiasis (sleeping sickness) is caused by *T. brucei* infection (**Figure 3**). *T. brucei* undergoes meiosis within the salivary glands of its tsetse fly vector. Meiosis appears to be a normal part of the developmental cycle of *T. brucei* [49–51]. Three proteins that are only known to express during meiosis, Dmc1, Mad1 and Hop1, are found to be expressed in the nucleus of a small fraction of dividing epimastigote trypanosomes in the salivary glands and nowhere else [51, 52]. Haploid gametes produced by meiosis can subsequently undergo pairwise interaction leading to cell fusion [49].



Figure 3.
Trypanosoma brucei [48].

Tsetse flies are able to resist trypanosome infection by mounting immune defenses [50]. The flies' defenses include the ability to produce increased levels of reactive oxygen species (ROS) such as hydrogen peroxide [51, 53]. ROS can cause DNA damage, including double-strand breaks. *T. brucei* can carry out homologous recombinational repair of double-strand breaks [54]. Such a repair process is likely facilitated in *T. brucei* by homologous chromosome pairing during meiosis. This process may help protect *T. brucei* against the assault by ROS mounted by the tsetse fly host.

Trypanosomes are classified in the supergroup *Excavata* that are one of the earliest diverging eukaryotic lineages [55]. The discovery of a sexual stage in *T. brucei* supports the idea that meiotic sexual production is an ancestral characteristic of eukaryotes [49] (see Section 1).

9. *Neurospora crassa*

The Ascomycete *Neurospora crassa* grows vegetatively as a haploid filamentous fungus. **Figure 4A** illustrates a segment of haploid hyphae which form a mass of

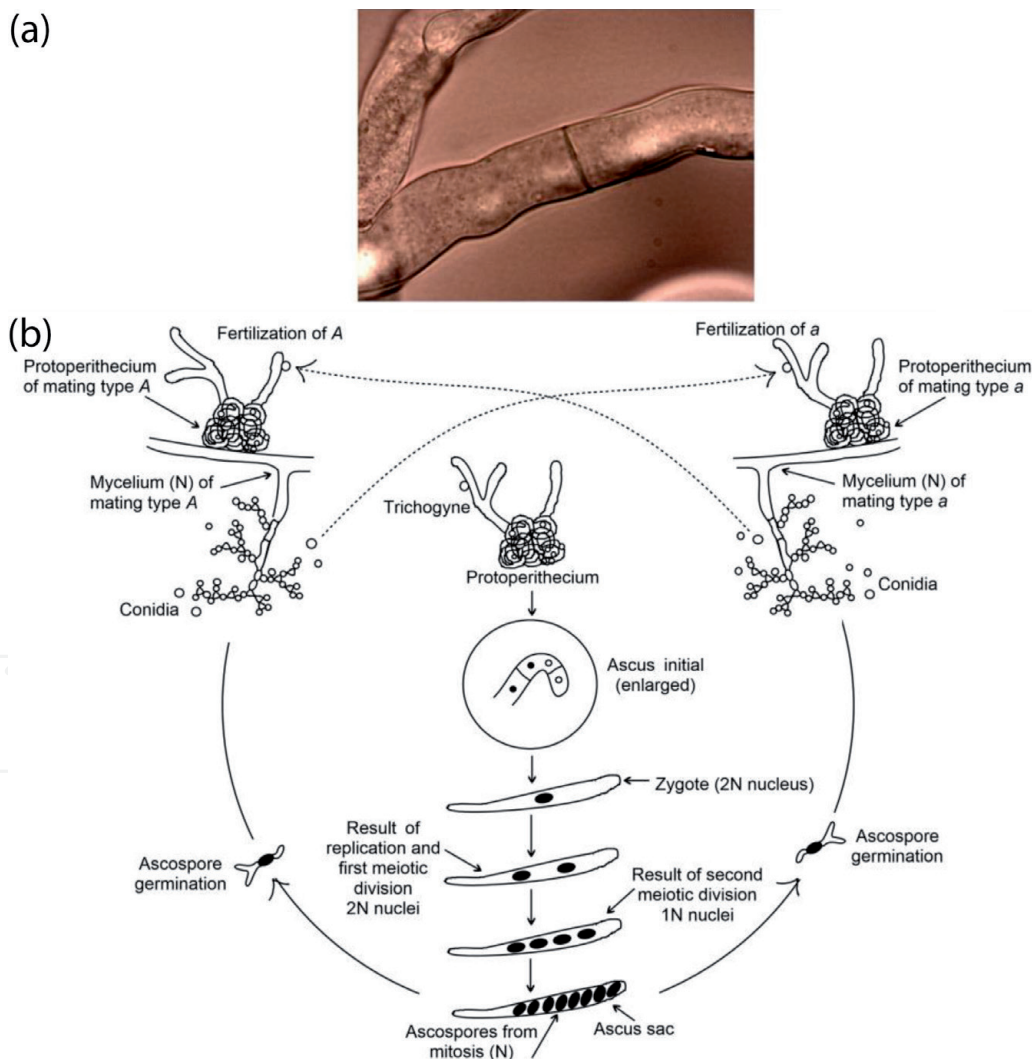


Figure 4. (A) *Neurospora crassa* hyphae [58], (B) *Neurospora crassa* life cycle. The haploid mycelium reproduces asexually by two processes: (1) simple proliferation of existing mycelium, and (2) formation of conidia (macro- and micro-) which can be dispersed and then germinate to produce new mycelium. In the sexual cycle, mating can only occur between individual strains of different mating type, A and a. Fertilization occurs by the passage of nuclei of conidia or mycelium of one mating type into the protoperithecia of the opposite mating type through the trichogyne. Fusion of the nuclei of opposite mating types occurs within the protoperithecium to form a zygote (2N) nucleus [59].

thread-like filaments comprising the mycelium which is the vegetative part of the fungus. The life cycle of *N. crassa* is outlined in **Figure 4B** which indicates the structures and events of sexual reproduction. Like *S. cerevisiae*, *N. crassa* has two mating types. Sexual interaction in *N. crassa* can only occur between individuals of opposite mating type. The diploid stage is very brief, occurring just prior to entry into meiosis. However, the brief diploid stage of *N. crassa* involves considerable complexity. The haploid vegetative multicellular filamentous stage, although longer lasting and larger than the diploid stage, has a relatively simple modular structure. In natural populations, recessive mutations specifically affecting the diploid stage are quite frequent [56]. Such diplophase specific mutations, when homozygous, can cause barren fruiting bodies (perithecia) and failure to form asci. Homozygous mutations can also lead to an abnormal meiosis with faulty pachytene or diplotene stages, or defective chromosome pairing [57]. At least 435 genes were estimated to affect the diploid stage [56]. This is at least 4% of the total 9730 genes of *N. crassa*. Thus it appears that the requirement for union of opposite mating types provides the adaptive benefit, in the diploid stage, of allowing the masking of deleterious recessive mutations (complementation) while also promoting the recombinational repair benefits of meiosis.

Species of *Neurospora*, including *N. crassa*, have life cycles adapted to ecosystems arising as the result of fire [60]. *Neurospora* species are common primary colonizers of trees and shrubs that have been killed by fire in Western North America. Fire appears to provide heat and chemical byproducts necessary for germination of ascospores that have been produced by sexual reproduction. Also fire can create a sterile environment with an abundance of nutrients derived from dead plant tissues upon which *Neurospora* can grow. The distribution of *Neurospora* growing at natural sites suggests that initial colonization by heat resistant ascospores is followed by vegetative growth, the production of conidia and then the dispersal of the conidia.

10. Amoebozoa

The *Amoebozoa*, a phylum within the kingdom *Protozoa*, contains about 2400 described species. Amoebozoan species include a variety of lineages of polymorphic amoeboid forms that until recently were considered to be asexual. A recent study, however revealed that amoebozoans representing all major subclades possess most of the genes that function specifically in meiosis, as well as many of the genes involved in meiotic recombinational repair [61]. It was concluded that *Amoebozoa* is ancestrally sexual. Since the *Amoebozoa* diverged in eukaryotic evolution before 720 million years ago [62], these findings suggest that meiotic sex was present early in eukaryotic evolution.

Another analysis of the *Amoebozoa* also supported the probable occurrence of syngamy (cell fusion) and meiotic processes in all major amoebozoan lineages [63]. This study concluded that most amoebozoans are likely capable of a canonical meiotic process. As one example, wild populations of the social amoeba *Dictyostelium discoideum* undergo widespread mating and sexual reproduction including meiosis when food is scarce [64, 65]. The evidence for the occurrence of meiotic sex among the amoebozoa is consistent with the general idea (see Section 1) that meiotic sex is likely a primitive characteristic of eukaryotes.

11. Eukaryotic sexual processes likely arose in the archaea

From about 3.4 billion to 570 million years ago, microbes were the only forms of life. The last common ancestor of all eukaryotes arose before 1.5 billion years ago [66].

The eukaryotic common ancestor is considered to have arisen when an anaerobic host archaeal cell acquired an internalized aerobic bacterium [67]. The internalized aerobe eventually evolved into the mitochondrion, providing the capability for respiration. The ancestral archaeal genome appears to have contributed more important genes to the eukaryotic nuclear genome (such as those genes involved in transcription, translation and replication) than the internalized aerobe [68]. Meiotic sex appears to be a primordial characteristic of eukaryotes (see Section 1). This suggests that sexual processes may already have been present in the archaeal microbe from which eukaryotes arose. Extant archaeal species such as *Sulfolobus solfataricus* and *Sulfolobus acidocaldarius* as well as several other archaeal species undergo interactions that have key features similar to sexual processes in microbial eukaryotes [69].

For instance, the hyperthermophilic archaeon *S. solfataricus* expresses the RadA protein, a homolog of the eukaryotic proteins Rad51 and Dmc1 that catalyze DNA pairing and strand exchange, central steps in recombinational repair during meiosis [70]. Exposure of *S. solfataricus* to DNA damaging UV irradiation or agents that cause DNA double-strand breaks induces pilus formation leading to cellular aggregation [71]. UV-induced cellular aggregation mediates high frequency chromosomal marker exchange between cells [72]. The DNA damage inducible DNA transfer process and subsequent homologous recombination were hypothesized to represent an important mechanism for providing increased repair of damaged DNA via homologous recombination in order to maintain genome integrity [71–73]. Van Wolferan and collaborators [74, 75] also obtained evidence with *S. acidocaldarius* that led them to propose that DNA transfer occurs in order to repair DNA damages by homologous recombination. Thus it appears likely that key elements of eukaryotic meiosis, namely the coming together and intimate alignment of chromosomes from different cells followed by repair of DNA damage by homologous recombination, already existed in the archaeal ancestors of eukaryotes. To some extent, these key elements are also present in many extant eubacteria, particularly in those species capable of natural genetic transformation [1]. This suggests that sexual processes were even present in a common ancestor of both eubacteria and archaea.

12. Conclusions

Meiotic sex appears to be a primordial characteristic of microbial eukaryotes and has likely provided a continuous adaptive benefit for as long as 1.5 billion years in diverse lineages of microbial eukaryotes. Since eukaryotes appear to have evolved from an archaeal ancestor, the adaptive function of sexual processes, even in archaeal species, is relevant to understanding sexual processes in microbial eukaryotes. In the archaea, homologous recombinational repair of DNA damages appears to be the principal adaptive benefit of sexual processes. Conclusions bearing on the adaptive benefit of sexual processes (syngamy and meiosis) in microbial eukaryotes are summarized below.

The dikaryotic fungi (*Ascomycetes* and *Basidiomycetes*) include some of the most well-studied microbial eukaryotic species with respect to sexual reproduction. Wallen and Perlin [76] concluded in a 2018 review of the function and maintenance of sexual reproduction in the dikaryotic fungi that sexual reproduction, including its central feature of homologous recombination, evolved to repair DNA damages that arise particularly from environmental stresses. In the ascomycete yeast *S. cerevisiae*, DNA repair by homologous recombination during mitosis is well established. Recombinational repair during meiosis is stimulated under starvation conditions and appears to be even more efficient than during mitosis. In natural populations of *S. cerevisiae* and *S. paradoxus*, the great majority of matings that occur are between

closely genetically related individuals. Thus sex in these species is unlikely to be primarily maintained by an adaptive benefit of producing genetic variation.

The ascomycete *S. pombe*, like *S. cerevisiae*, tends to mate when nutrients are scarce. Introduction of DNA damage by different DNA damaging conditions stimulates sexual reproduction and meiotic recombination, consistent with the idea that meiotic recombination is an adaptation for repair. Another ascomycete, *C. albicans* is regarded as a parasexual, rather than sexual, species since it appears to undergo a meiotic process that is not associated with the organized chromosome segregation that normally results in haploid meiotic products. Nevertheless *C. albicans* contains a set of genes homologous to genes that function in meiosis in other species including a key gene that only functions in meiosis. Same sex mating in *C. albicans* likely occurs frequently in nature especially under environmental stress conditions. *U. maydis* is a basidiomycete fungus. Upon infecting its plant host it can undergo meiosis. Recombinational repair occurring during meiosis likely helps protect the *U. maydis* genome from oxidative attack by the plant host's defensive system against invading fungal pathogens.

Paramecium tetraurelia, a unicellular ciliate, undergoes clonal aging over successive asexual generations leading eventually to extinction. However, if aging paramecia are allowed to undergo a sexual process, either conjugation (mating with another individual) or automixis (self-fertilization), the progeny have a lifespan characteristic of youthful paramecia. During clonal aging DNA damage dramatically increases. Presumably, during automixis or conjugation, age-related DNA damage is repaired by homologous recombination.

Volvox carteri is a facultatively sexual colonial green algae. Sex (syngamy and meiosis) can be induced by conditions that cause oxidative stress, suggesting that sex may be a response to oxidative DNA damage.

T. brucei is a trypanosome parasite that causes human sleeping sickness. The tsetse fly acts as a vector for transmitting the parasite. *T. brucei* after infecting the fly is able to undergo meiosis in the fly's salivary glands. The tsetse fly can defend itself against *T. brucei* infection, in part, by producing DNA damaging reactive oxygen species. When the trypanosomes within the fly's salivary glands undergo meiosis, the associated homologous recombination likely promotes repair of the oxidative damage in the trypanosome's genome.

The amoebozoa are a phylum of protozoans that diverged early in eukaryotic evolution. The amoebozoa include a large number of species that are classified into major subclades. Representative species from these subclades were recently found to have many genes that are related specifically to meiosis and to recombinational repair. This finding suggests that most amoebozoans are likely capable of meiosis, and contributes further to the idea that sex is a primitive character of eukaryotes.

Sexual processes in microbial eukaryotes are often induced by stress. In addition to the examples described above, sexual processes have also been demonstrated to be inducible by stress in other microbial eukaryotes. As an example, when *Chlamydomonas reinhardtii*, a unicellular green alga, is grown in a medium with limiting nitrogen, it differentiates to form gametes that are able to fuse together to produce a zygote capable of meiosis [77]. As another example, when the hyphae of the oomycete *Phytophthora cinnamomi* are exposed to hydrogen peroxide or mechanical damage, sexual reproduction is induced [78]. Also, meiotic processes can be induced in the human fungal pathogen *Cryptococcus neoformans* by desiccation or nitrogen starvation [79].

As noted in Section 1, the main focus of this review is to understand the principal adaptive function of meiotic sexual reproduction in microbial eukaryotes. The evidence reviewed in the preceding sections suggests that meiotic homologous recombination, the central process of meiosis, is an adaption for repairing DNA

damages. The need for repair of DNA damages may be particularly critical in response to stress. The alternative possibility, that meiotic sex is primarily an adaptation for generating genetic variation seems less plausible because in well studied microbial eukaryotes, such as *S. cerevisiae* and *S. paradoxus*, all but a small percentage of matings in nature are between clonally related individuals. Nevertheless, the existence of mating types as in *S. cerevisiae*, *N. crassa* and other microbial eukaryotes suggests that some degree of out-crossing is adaptively beneficial. The benefit of out-crossing is that it promotes complementation, the masking of deleterious recessive mutations in diploid cells [80]. This masking benefit of out-crossing is generally recognized as underlying such concepts as heterosis, hybrid vigor or the avoidance of “inbreeding depression” [81]. Also, sexual processes can produce genetic variation that may be beneficial, as in the case of *C. albicans* populations where parasexual recombination can apparently facilitate, over successive generations, the evolution of resistance to the antifungal agent fluconazole [38].

Conflict of interest

Both authors declare that they have no conflict of interest.

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